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Future of the nerve fibres imaging: tractography application and development directions

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Tractography is a tool available in a growing number of centres, to enable planning of neurosurgical interventions. This method has some drawbacks and due to its increasing availability is causing a growing controversy over the possibility of an anatomical mapping of the nerve fibres. This article aims at summarising the application of the diffusion magnetic resonance in contemporary neurosurgery method, showing the usefulness and merits of its performance before surgical procedures, limitation of its application and recommendations for its improvement and more effective use for diagnostic purposes. (Folia Morphol 2015; 74, 3: 290–294)

Key words: diffusion tensor imaging, neurosurgery, nerve fibres imaging

INTRODUCTION

It has been barely 20 years since the imaging of nerve fibres *in vivo* is possible. Previously their course was studied only *post mortem,* using histochemical staining methods. These methods were a good tool to analyse the course of the fibres, but did not apply for the diagnosis and treatment of the diseases [1]. The breakthrough was use of diffusion tensor imaging (DTI) and magnetic resonance diffusion. It enables non-invasive study of nerve bundles in the white matter, allowing their different courses to be compared. With the availability of this technique correlations between clinical symptoms and changes in diffusion resonance imaging could be sought. This method is based on the magnetic resonance imaging (MRI) examination, although with measurement of water molecules diffusion through the cell membrane. In tissues which run parallel, diffusion vector of water molecules is anisotropic and thus propagates in the same direction. In contrast to isotropic diffusion vector (in every possible direction), the anisotropy of diffusion can be imaged [9].

The neural pathway course is anterior-posterior, lateral-medial or upper-lower. Measurement of MRI diffusion is made in the individual voxel (value on a regular grid in 3-dimensional space). Due to the complex nature of the brain, the course of the fibres in the voxel is rarely purely parallel. In most cases, it is a group of fibres crossing to a certain extent. In case of the measurement of nerve fibres, accumulated vector of the diffusion is taken into account. This gives not entirely true picture of all fibres, calculating a mathematical average of their course. In case of the two major directions of the diffusion, mathematical average of this two will be shown, which will not picture properly either of two intersecting fibre bundles. For this reason, work began on the change of the mathematical model of diffusion tensor. Currently there are at least several known models, such as the mixture of tensors, spherical deconvolution and diffusion spectrum. At present, there are no confirmed tests on a sufficiently large group of patients that can proof superiority of one mathematical model over the other. It seems

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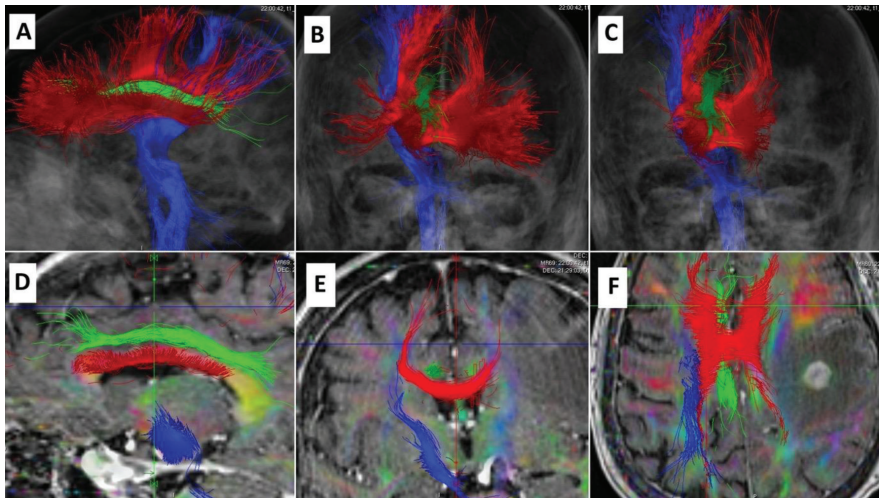

Figure 1. Directionally encoded colours (DEC); **A, B, C.** Three-dimensional model; **A, D.** Sagittal plane; **B, C, E.** Coronal plane; **F.** Axial plane. Each direction of a neural pathway is encoded by a separate colour: red describes left-right direction (commissural pathways), green shows anterior-posterior pathways (association white matter) and blue colour codes caudal-rostral direction (projection fibres).

that a high chance for the dominance has a spherical deconvolution model which tries to differentiate and illustrate intersecting neural pathways, thereby giving a more complete picture of their course. Compared to DTI, main pathways of white matter, such as the pyramidal tract, had a completely different shape in their trajectory. In particular, voxels' fragments of pyramidal tract appeared, that were not imaged in case of DTI MRI due to crossing fibres (Fig. 1).

DTI MRI allows more accurate analysis of data using specific parameters such as mean diffusivity (MD) and fractional anisotropy (FA). MD represents an average diffusion of water molecules in a given region of interest, while the FA determines how much the diffusion is isotropic or anisotropic in the particular voxels. Values closer to one are darker, whereas values closer to zero are brighter. The higher the anisotropy, the greater the amount of normal fibres running parallel. Analysis of these parameters provides information not only about the course of the fibres, but also about the efficiency of diffusion in the given voxels, thereby detecting the damage of the fibres or hypoxia.

APPLICATION

DTI MRI can be used in the planning for resection of the pathologic lesion in the brain, where in conjunction with the neuronavigation, it gives the surgeon intraoperatively the image of the nerve fibres in the immediate vicinity of the tumour, thus allowing for choosing the safest neurosurgical access. It is also used after surgery. Using DTI MRI study, we can compare surgical accesses to pathologic lesion and calculate in which of them the largest amount of nerve fibres would be destroyed. We are able to compare parameters such as the volume of the particular fibres damaged during surgical access and measurement of the length of the fibres. DTI MRI, together with the clinical data of the patient, gives a complete picture of the surgery result (Fig. 2) [2, 10, 11].

Neurons are cells extremely sensitive to hypoxia. In case of ischaemic stroke, it takes relatively long time to visualise ischaemic changes in the brain tissue, when using MRI. Damage to cell membranes causes impairment of diffusion and reduces apparent diffusion coefficient (ADC) values. Early hypoxia causes cell swelling which contributes to diffusion impairment in these cells. Therefore the DTI MRI use is advantageous for the early diagnosis of ischaemic stroke.

For over two decades, various works were created on the basis of diffusion MRI. The changes in nerve fibres anatomy in the population were studied [5, 8, 15]. Differences in the anatomy of the nerve fibres in bipolar disorder were found, thereby paving the way for the diagnosis of mental illnesses and their aetiopathology [7]. Diffusion parameters were lower (decreased ADC) in aging population [13]. The challenge for the DTI was to explore the fibres within the spinal cord. Diagnosis was difficult, because of the small cross-sectional area of the spinal cord, artefacts related to sensitivity testing, respiratory movements and the heartbeat. Thanks to the im-

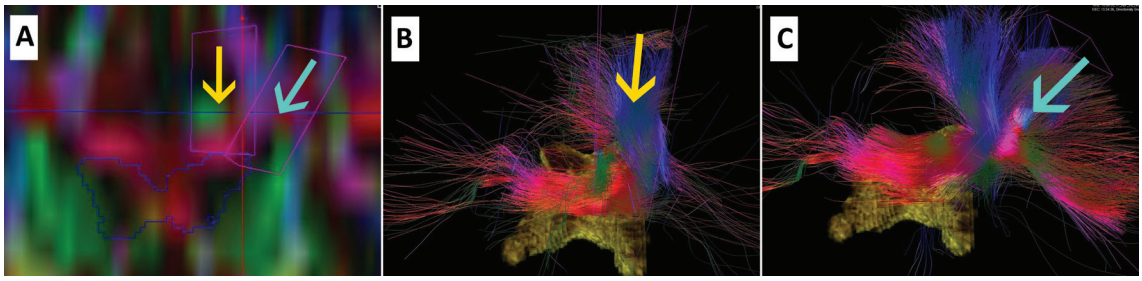

Figure 2. The application of diffusion tractography (diffusion tensor imaging — DTI) to neurosurgical approach selection. **A.** Coronal plane presenting two approaches to the lateral ventricle (delineated in blue). **B, C.** Three-dimensional models of trans-F1 (yellow arrow) and trans-F2 (blue arrow) approaches. The selection between the accesses to the lateral ventricle can be successfully based on DTI. Different numbers of either projecting, association or commissural pathways are disrupted by these two approaches (**A–C**).

provement of the diffusion MRI protocols, imaging in this area also became possible. In patients with post-traumatic interruption of the spinal cord, it is not always possible to visualise the loss of continuity in T2 dependent imaging. DTI MRI is helpful in differentiation, showing a significant reduction in the level of anisotropy of spinal cord injury. Correlation between the severity of the destruction of the spinal cord and diffusion disruption in the tissue below and above spinal cord damage is also noticeable. After injury, there are several processes that occur inside spinal cord that can be visible in DTI, such as demyelination, remyelination and atrophy of nerve cells. In patients with myelopathy of the cervical spine, in the case of spondylosis, there is a gradual degeneration of the spinal cord that can be imaged with MRI T1 and T2 only in advanced stage of the disease. Earlier stages of damage are visible on diffusion MRI.

This study is also helpful in planning treatment for patients with proliferative process inside the spinal cord, since it allows differentiation between malignancy and an active inflammatory process [14].

DTI MRI is the only available method for the imaging of nerve fibres *in vivo*, which means that there is no alternative study that can be used for imaging neuronal tracts. However, this study has several disadvantages. Very weak possibility to differentiate crossing fibres and those with curved course is essential. Examination and scan processing are also important. There are limitations due to the software provided by the manufacturer. The test is subjective and depends on the person preparing it, the choice of region of interest and software provided by the manufacturer. Incorrect region of interest selection will cause inappropriate selection of the nerve bundles, some of them will not be visible or will be wrongly assigned to the bundle of fibres which does not contain them anatomically. Another problem is difficulty in identifying tracts in the area of oedema around pathological mass. Imaging of the smaller nerve fibres is also difficult. Number of bundles extending in parallel must be large enough to make it possible to visualise them (Fig. 3).

By analysing neural pathways we gain information about their course, but it is not sufficiently detailed information. For example, the superior-posterior course of the fibres does not differentiate afferent from efferent fibres, instead it provides only general information about the direction of their course [3]. All these aspects limit to some extent the use of DTI. However, due to the lack of an alternative *in vivo* method, it is necessary to improve this one. Some studies describing tractography preparation before surgery are critical value of its application. On the other hand, this test is widely used to handle neurosurgical planning in many medical centres.

Tractography is also used in planning neurosurgical treatment of drug-resistant epilepsy. In this case, resection of brain cortex area responsible for uncoordinated neuronal discharges is performed without damaging eloquent areas. Choosing the right area to be resected allows avoiding complications such as neurological symptoms after surgery. According to the Piper et al. [12], DTI has helped modify medical procedures for resection of the 1/4 occipital, 1/3 frontal, 2/3 of the parietal lobe and multilobar resections.

The use of tractography in many realms of neurosurgery also gives smaller exponents of neurological complications in patients after surgery. Its usefulness has already been substantially proven. However there are reports trying to prove inadequate presenta-

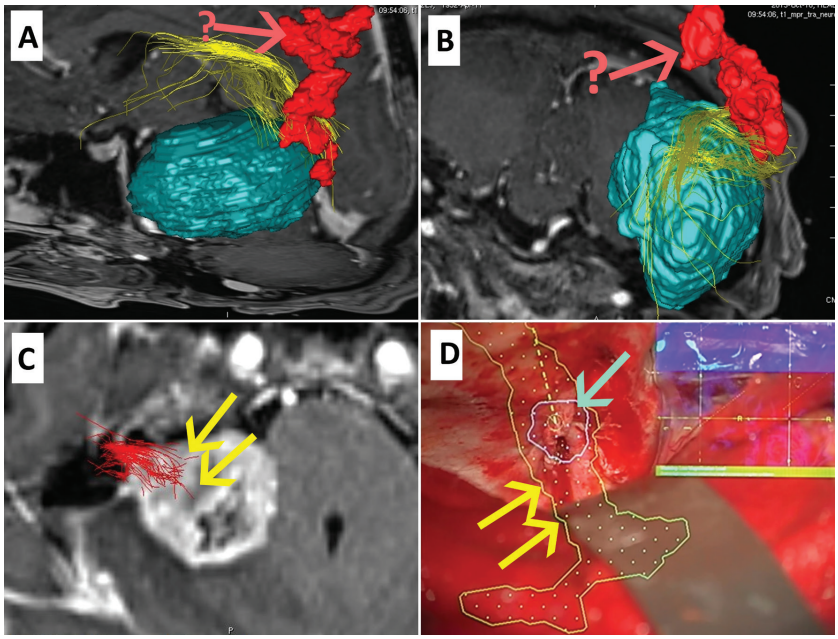

Figure 3. Diffusion tractography (diffusion tensor imaging — DTI) does not represent real white matter pathways. Sagittal (**A**) and coronal (**B**) planes of a left temporal lobe tumour (blue model). Wernicke area (red model) is estimated by means of functional magnetic resonance imaging (MRI). Arcuate fasciculus (pictured with yellow) terminate only at a part of the Wernicke area (red arrow with a question mark), suggesting the possible inaccuracy in DTI and/or functional MRI method. Several methodological limitations of DTI method refer also to visualising cranial nerves, including (**C**) facial nerve (yellow arrows) bending over a cerebello-pontine angle neuroma and (**D**) optic nerve (yellow arrows) distorted by a small schwannoma (blue arrow).

tion of nerve fibres. Shawn Farquharson et al. [6] in their article describe improper mathematical model illustrating the diffusion and proposes spherical deconvolution model and showing the difference when assessing the tumour edges during preoperational preparation for resection of pathologic lesion. These borders in the case of these two methods differ significantly. When using DTI model, it was possible to picture significantly less nerve fibres of corticospinal tract, thereby changing surgical access to resected lesion. Spherical deconvolution model differentiates between intersecting nerve fibres in the given voxel. In case of the DTI model, average vector of crossing fibres is drawn, giving an incorrect picture. On the basis of the article, Farquharson et al. [6] compared the mathematical models, DTI and spherical deconvolution, with the course of the fibres observed postmortem in human brain tissue and on that basis conclude that the use of spherical deconvolution model shows nerve fibres more accurately. This method, although in the initial phase draws promising future of diffusion MRI; however, without doubt requires confirmation in clinical trials that compare these two models.

FUTURE OF DIFFUSION MAGNETIC RESONANCE

Diffusion MRI is a still growing field. Mathematical model presenting diffusion in space is constantly changing to visualise more accurately nerve fibres, with an increase of power of magnetic resonance field and elimination of artefacts. It also became possible to plan within the spinal cord. This method, despite its drawbacks will certainly not be abandoned, because to a large extent we can eliminate these disadvantages, aiming at making the most adequate representation of the nerve fibres. Perhaps, on the basis of today's research, it will be possible to develop a universal mathematical model allowing adequate mapping the course of the nerve pathways. A major problem seems to be lack of clarity of the importance of nerve pathways in the brain. It is known that large amount of fibres, when damaged as a result of the destruction or pathological processes, or even as a result of the surgical approach, does not produce any symptoms. On the basis of the destruction of these fibres and observation of neurological deficits, we try to infer their meaning. The mere possibility of constructing researches based on neural bundle injury and observation of neurological

deficits, is restricted to an absolute minimum damage of fibres needed for a given surgical procedure and therefore does not give a full picture of the relevance of fibre bundles. On the basis of these data, DTI MRI atlases were created, allowing surgeon to move more efficiently in white matter [4]. Many clusters of fibres can be damaged with minimal presentation

Diffusion MRI, despite its imperfection, is a very valuable tool, used only recently; therefore it is not yet fully optimised. Improvements that come every year are making this method more useful, allowing for more accurate imaging with the exception of the error and artefacts accompanying the study. The development of technology has affected not only the development of MRI devices themselves, but also to the appropriate software and a mathematical model. There are some limitations of this method, which will not be adjusted because of the specific nature of diffusion as physical process. However, as a method which does not have competitive examination, it continues to meet the demands placed upon it's goals.

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